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Review

Immunopathology of Behcet's Disease: An Overview of the Metagenomic Approaches

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Abstract: The impact of the microbiota residing in the body on local and systemic immune responses has been increasingly recognized. The major gut microbe metabolites' short-chain fatty acids (SCFAs) are suggested to regulate the balance between regulatory (Treg) cells and helper T 17 (Th17) cells in physiological and pathological conditions by enhancing regulatory T (Treg) cell function through epigenetic modifications. Patients with Behcet's disease (BD) exhibited enhanced Th17 cell-mediated immune responses and decreased intestinal relative abundances of SCFA-producing bacteria. Causal correlations between aberrant immune responses and gut microbial composition in patients with BD have been reported in Italy, the Netherlands, Turkey, China, and Japan. We reported that the gut and oral microbiota profiles of patients with BD shared some common features. Immune responses against both commensal and pathogenic microbes may play a crucial role in BD development. This review summarizes the current literature, which was retrieved from public databases, such as PubMed and MEDLINE using search terms, including Behcet's disease, helper T cells, and microbiota, during 1970–2022, on the potential functional correlation between immune cells and microbiota in patients with BD.

Keywords: Behcet's disease; Bifidobacterium; butyrate; IgA-seq; microbiota; propionate; secretory IgA; short-chain fatty acids; Th17 cells; Treg cells

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1. Introduction

Behcet's disease (BD) is a chronic and multisystem inflammatory disorder characterized mainly by recurrent oral and genital ulcerations, repeated attacks of uveitis, and erythema nodosum-like skin lesions [1]. The incidence of BD varies depending on the geographical region. In particular, the prevalence of BD is high in the ancient Silk Road, which includes Italy, Turkey, Israel, Saudi Arabia, Iran, China, Korea, and Japan [2]. HLA-B51 has been detected in approximately 50% of patients with BD [2]. Genome-wide association studies (GWAS) have identified HLA-B51 and ERAP1 as genetic susceptibility factors for BD [3–5]. Environmental factors, including several microorganisms, are reported to mediate the pathogenesis of BD [1,2].

In the data of the International Classification of Disease in the United States, the mean hospital length of stay was higher in patients with BD than those in the general population with an admission diagnosis of sepsis, pneumonia, and left upper limb cellulitis [6]. Poor oral health is often correlated with severe BD [7]. For example, *Streptococcus sanguinis*, which causes dental plaque, is frequently detected in the oral cavity of patients with BD [8]. Conventional sterilization procedures decrease pathergy reactions in patients [9]. This indicates that the skin commensal microbes are associated with the severity of the reaction. Bacterial heat shock proteins (HSPs) exhibit a high degree of sequence homology with mammalian HSPs. Immunoreactivity to HSPs is postulated to be a potential mechanism of

BD-related inflammation [10]. Lymphocytes from patients with BD strongly react with the HSP of *Mycobacterium bovis* compared with those from healthy individuals and patients with other immune diseases such as systemic lupus erythematosus and Sjogren's syndrome [10].

Recently, the correlation between microbiota and the host immune system was reported to be stronger than was previously assumed. Culturable bacteria and their genes have been identified in human fetal organs, such as the gut, skin, and lungs, from the second trimester of gestation [11]. T cells in the fetal mesenteric lymph nodes react with both several bacterial strains and bacterium-primed dendritic cells during gestation [11].

Tumor-bearing mice gavaged with 11 bacterial strains exhibited enhanced interferon (IFN)-γ production by T cells. Additionally, the effects of immune checkpoint inhibitors were potentiated in these mice, potentially through bacterial antigen-induced T cell expansion [12].

Short-chain fatty acids (SCFAs), which are major gut microbial metabolites, are produced through the fermentation of dietary fibers [13]. Previous studies have reported that SCFAs promote regulatory T (Treg) cell differentiation in mouse models via epigenetic modification [14–17] and ameliorate the disease activities of colitis [14–16], arthritis [17], and encephalomyelitis [18]. Skewed T cell responses and altered gut microbial composition are reported in several human immune disorders [19,20].

This review summarizes the current understanding of the potential functional correlation between immune cells and microbiota in patients with BD. These host and bacterial factors of patients with BD have been suggested to share some common characteristics in different countries.

2. Search Methods

A literature review was performed using the following terms: "Behcet's disease", "helper T cells" (retrieved 199 articles with the term "Behcet's disease"), "gut microbiota" (31 articles), "oral microbiota" (13 articles), "genome wide association study (GWAS)" (96 articles), "single nucleotide polymorphism (SNP) genotyping" (99 articles), "secretory IgA" (7 articles), "short chain fatty acids" (13 articles), "food supplements" (12 articles), "functional food" (6 articles), "herbals" (30 articles), and "medicine" (15 articles were retrieved with the terms Behcet's disease and intestinal bacteria). Relevant original and review articles were collected through the PubMed, MEDLINE, Cochrane library, and Scopus databases between March and June 2022.

3. Immunopathology of BD

3.1. Lymphoid Cells

The most characteristic feature of the early stage of inflammation in BD is vasculitis with neutrophil infiltration near lesions, such as oral and genital ulcers, cutaneous erythema, and uveitis [1]. HLA-B51 and helper T 17 (Th17) cells are crucial factors for neutrophil activation [2].

3.1.1. Th Cells

Naive Th cells differentiate into functional effector Th cells depending on the local immune environmental conditions, including cytokine and chemokine levels. Differentiated Th cells are classified into four subsets (Figure 1) [21,22].

The concepts of Th1 and Th2 were initially proposed based on the characterization of effector cytokines and their functions [23]. Th1 cells induce the monocyte/macrophage-mediated immunity of monocytes/macrophages through the secretion of IFNγ. Meanwhile, Th2 cells promote humoral immunity and antibody production through the secretion of interleukin (IL)-4 and IL5.

Th17 cells, which are characterized by the presence of the inducing cytokine, IL23, activate epithelial cells and neutrophils through IL17 secretion. Treg cells suppress Th cell function by secreting transforming growth factor (TGF)-β and IL10. The differentiation of

Th17 and Treg cells involves common processes, especially the generation of Th17/Treg progenitor cells (Figure 2) [24]. Th17 and Treg cells are often activated in the intestine [22].

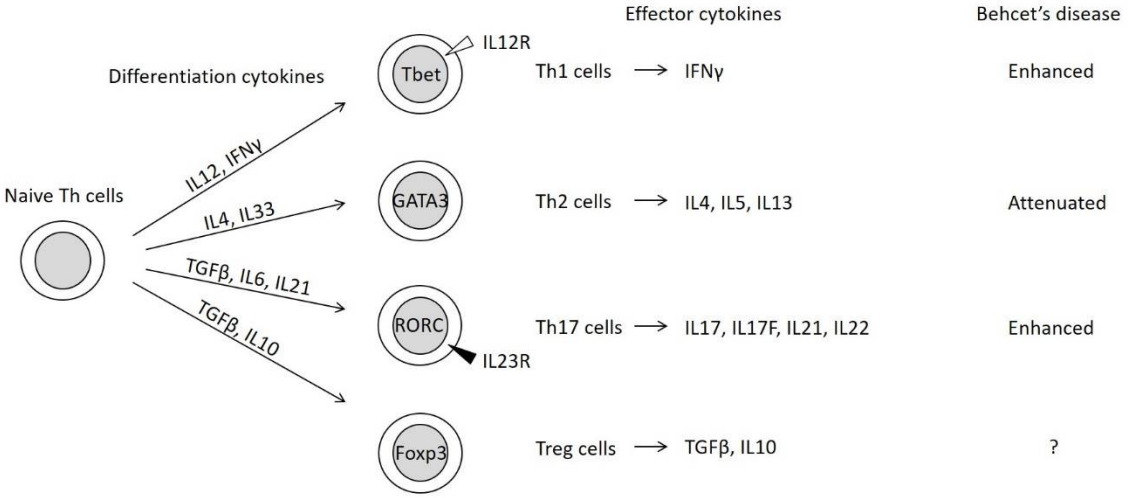

Figure 1. Four subsets of differentiated helper T (Th) cells [21,22]. Naive Th cells differentiate into functional effector Th cells through the activities of differentiation-related cytokines and the expression of master transcription factor genes (represented within the circles). The master transcription factors repress the expression of alternate Th cell subset-related transcription factors [21]. IL12R, IL12 receptor; IL23R, IL23 receptor.

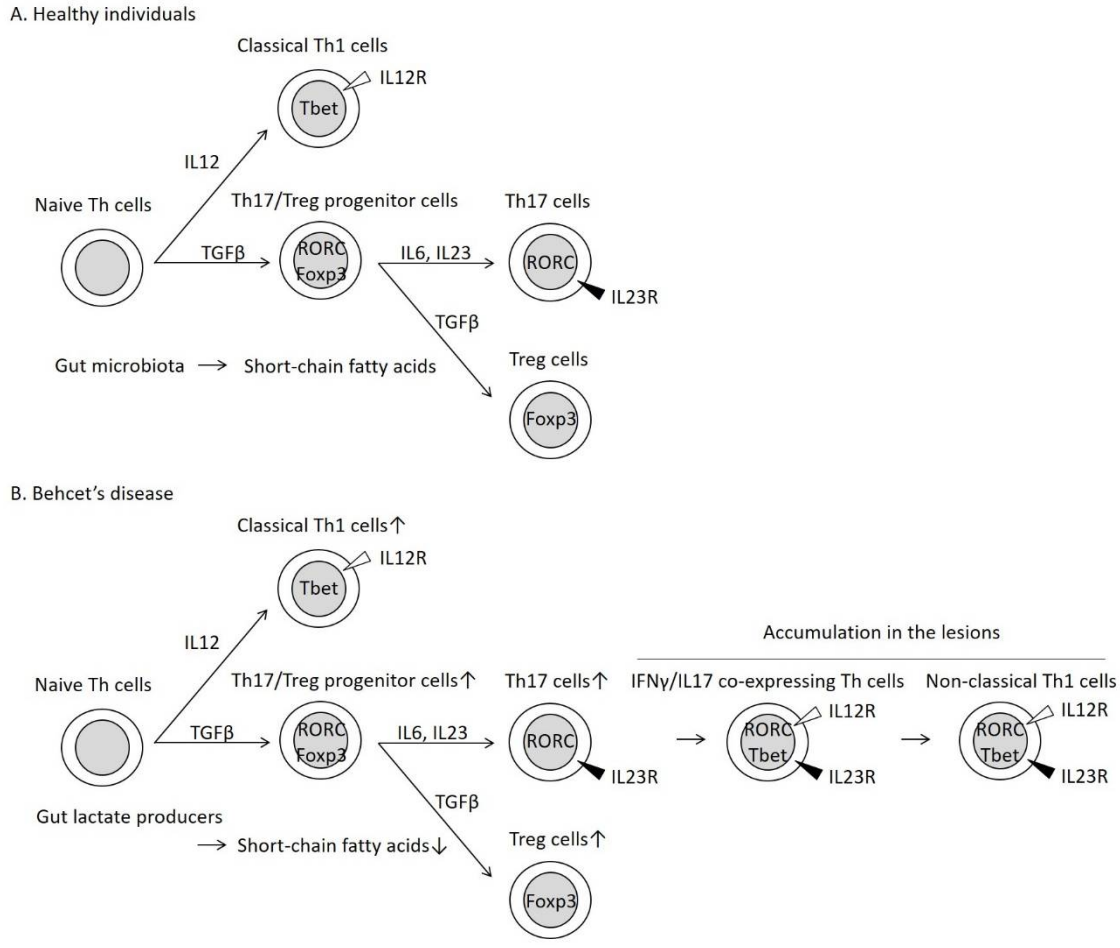

Figure 2. Helper T 17 (Th17) cell differentiation into IFNγ/IL17 co-expressing Th cells and non-classical Th1 cells in patients with Behcet's disease (BD). In healthy individuals (**A**), naive Th cells

differentiate into classical Th1 cells through the activities of IL12 [21]. In the presence of TGFβ, naive Th cells are transformed to Th17/Treg progenitor cells, which subsequently differentiate into Th17 cells through the activities of inflammatory cytokines, such as IL6 and IL23 [24]. The same progenitor cells can differentiate into Treg cells without inflammatory cytokines [24]. In patients with BD (**B**), Th17 cells are unstable in the inflammatory condition and are transformed into IFNγ/IL17-expressing Th cells and non-classical Th1 cells [25]. Non-classical Th1 cells are distinguished from the classical Th1 cells based on the expression of the cytokine receptors [25]. These inflammatory Th cells were observed simultaneously in the skin lesions of patients with BD [26]. Short-chain fatty acids (SCFAs) derived from gut microbiota stabilize the expression of the Treg cell master transcription factor Foxp3 [14–17] and promote Treg cell differentiation [14–18]. Decreased intestinal SCFAs may enhance skewed Treg cell differentiation in patients with BD.

Inflammatory cytokines, such as IL6 and IL23, promote Th17 cell differentiation from progenitor cells (Figure 2) [24]. In contrast, the same progenitor cells differentiate into Treg cells without inflammatory cytokines [24]. In the periphery, the fate of Th17 cells is unstable, and Th17 cells are transformed into IFNγ/IL17-expressing Th cells (Figure 2) and subsequently into IFNγ-expressing cells (non-classical Th1 cells) (Figure 2) [25]. These Th cells are reported to play an important role in both physiological and pathological immune processes [25]. Thus, Th17 and Treg cells maintain the balance between the pro-inflammatory and anti-inflammatory conditions in the intestinal tract [22].

Previous studies have reported that Th1 and Th17 cell functions are upregulated, whereas Th2 cell function is suppressed in patients with BD [27–45]. The numbers of Th17 cells and IFNγ/IL17-expressing Th cells are upregulated in the peripheral blood of patients with BD [30–33,35–42,44,45]. In addition, to effector Th cells, such as Th1, Th17, and IFNγ/IL17-expressing Th cells [26,27,33,34] and Treg cells [34], have been detected in the erythema nodosum-like skin lesions of BD. The number of Treg cells and the expression levels of Treg-cell-related genes in patients with BD were upregulated when compared with those in healthy donors [34,46]. In contrast, several studies have demonstrated that these Treg-associated components in patients with BD were downregulated in BD patients when compared with those in healthy individuals [38,44,47]. The expression levels of the IL17 and IL23 [43]/IL23 receptor [41] were positively correlated in the Th cells of patients with BD. In the presence of IL1β, IL6, IL23, TGFβ, and tumor necrosis factor (TNF)-α, the production of IL17 in the cultured peripheral Th cells derived from patients with BD was markedly upregulated when compared with that in the cultured peripheral Th cells derived from healthy individuals [41]. Thus, these data indicate that various components of the pathways shown in Figure 2 are simultaneously activated in patients with BD.

3.1.2. γδ T Cells and Innate Lymphoid Cells (ILCs)

γδ T cells express toll-like receptors and react with bacterial antigens to promote bacterial clearance [48]. Similar to Th17 cells, IL17-producing γδ T cells tend to migrate into mucosal tissues, such as the lungs and intestine [49], and induce the rapid infiltration of neutrophils into the lesions of *Escherichia coli*-infected mice [50] in the presence of IL23 [51]. Vγ9δ2+ T cells, which are a major subset of γδ T cells, recognize bacterial antigens [52], whereas Vδ1+ T cells react with the major histocompatibility complex class I-related chain A (MICA) expressed on the damaged intestinal epithelium [53].

The number of Vγ9δ2+ T cells was upregulated in the peripheral blood of patients with BD. Additionally, Vγ9δ2+ T cells produce TNFα and perforin granules [54]. One study demonstrated that the numbers of Vδ2+ T cells and Vδ1+ T cells were upregulated in the peripheral blood and bronchoalveolar lavage/cerebrospinal fluid, respectively, of patients with BD [55]. Furthermore, Vγ9δ1+ T cells react with *Streptococcus sanguinis* without an apparent HLA restriction [56]. These data suggest that γδ T cells may also be associated with the development of inflammatory responses in patients with BD.

A similar concept may aid in elucidating the role of ILCs in the pathogenesis of BD. ILCs, which are a subgroup of lymphocytes that lack antigen-specific receptors [57], are

divided into three subgroups, ILC1, ILC2, and ILC3. The ILC3 subgroup, which may function as the innate counterpart of Th17 cells, produces IL17 in the presence of IL23 [57].

The peripheral blood levels of the total ILCs and ILC3 in patients with active BD were higher than those in patients with inactive BD and healthy individuals [58].

Thus, these lymphoid cells can initiate BD inflammation by secreting IL17.

3.2. HSPs

Bacterial and mammalian HSPs share a high sequence homology [10,59]. Human HSP60 shares approximately 70% and 40% sequence homology with Chinese hamster HSP60 and mycobacterial HSP65, respectively. Bioinformatic analyses HSP65 has a high binding capacity to HLA-B51 [60].

In the presence of an HSP peptide derived from *Mycobacterium bovis*, the production of IFNγ, IL12, and TNFα in the peripheral blood lymphocytes of patients with BD was higher than that in the peripheral blood lymphocytes of healthy individuals [27]. Lymphocyte proliferative responses against mycobacterial HSP65 peptides and/or homologous human HSP60 peptides were observed in patients with BD residing in the United Kingdom [10], France [45], Turkey [61], and Japan [60,62]. HSP60 is expressed in the peripheral blood lymphocytes and intestinal tissues of patients with BD but not in those of healthy individuals [28].

These data suggest that bacterial HSPs mimic human HSPs and that cross-reactive T cells play a role in the pathogenesis of BD.

3.3. Pathergy Test

A positive pathergy test has been reported in approximately 30–60% of patients with BD [63]. Surgical sterilization of the skin decreases the positivity rates of tests in patients with BD [9]. The proportion of positive test results varied depending on the body areas with the highest proportion observed in the forearm [64]. Skin pricks with self-collected saliva samples increased the sensitivity of the test [65]. Meanwhile, needle punctures cause tissue damage in the eye [66] and blood vessels [67] in patients with BD. These data suggest that the overactivation of immune cells against multiple commensal microbes may contribute to the pathogenesis of BD.

The numbers of lymphocytes, monocytes, and neutrophils were upregulated in the skin lesions but were not markedly different between patients with BD and healthy individuals at 8 h post-needle prick [68]. At 48 h post-needle prick, the immune responses of the healthy donors were limited or slightly decreased, whereas the migration of the lymphocytes and monocytes was further enhanced in patients with BD. Gene expression analyses of skin tissues revealed that, in addition to Th1 responses (IFNγ and IL12), Treg responses (CD25 and Foxp3) were significantly upregulated in BD lesions [68], which was consistent with the results of previous studies that demonstrated the enhancement of both effector Th and Treg cells in patients with BD [34,46].

4. Potential Correlation between Microbiota and Immunopathology in BD

4.1. Gut Microbiota in Human Disease

Gut microbiota may be associated with the pathogenesis of human diseases, such as obesity, type 2 diabetes, non-alcoholic fatty liver disease, coeliac disease, inflammatory bowel disease, and colorectal cancer, mainly through the production of metabolites [69]. Microbial metabolites primarily comprise SCFAs, bile acids, and trimethylamine N-oxide (TMAO) in humans [69].

SCFAs, such as acetate, propionate, and butyrate, are produced through the bacterial fermentation of indigestible carbohydrates (dietary fiber) and are absorbed into epithelial cells as an energy source [13]. Based on physiological metabolism, SCFAs increase the expression of tight junction proteins [70]. A low-fiber diet reduces the colonic mucus barrier function owing to the prevalence of mucin-degrading bacteria [71]. High intestinal permeability in genetically engineered mucus-deficient mice increases susceptibility to

colitis with transmissible gut microbiota alterations in cohabitants [72]. The leakage of lipopolysaccharides from the intestine [72] may be related to type 2 diabetes, atherosclerosis, and several types of cancer [73,74].

In the gastrointestinal tract, enteroendocrine cells express receptors for SCFAs and secrete glucagon-like peptides (GLPs) and peptide YY in response to stimulation, suggesting a close relationship between intestinal SCFAs and host glucose metabolism [13]. Therefore, SCFAs in the intestine improve insulin secretion and the sensitivity of the host [73,74].

Similar protective effects on host glucose homeostasis have been reported in bile acid metabolism via the secretion of GLP1 and insulin [75]. A high-fat diet promotes the production of other major bacterial metabolites and secondary bile acids, which are reported to be associated with tumorigenesis, especially in the intestine [73,74,76].

Choline and L-carnitine in the intestine induce the production of trimethylamine (TMA), a newly discovered bacterial metabolite. Subsequently, TMA is bioactivated to TMAO in the liver under high-fat diet conditions [77]. The plasma level of TMAO is correlated with the risk of death, myocardial infarction, and stroke [78].

Thus, these data suggest highly complex interactions between bacterial metabolites and host organs in human diseases.

4.2. Physiological Correlation between Gut Microbiota and Th Cell Function through SCFAs and the Pathology of Rheumatic Diseases

SCFAs promote Treg cell differentiation via epigenetic modification of Foxp3 (Figure 2) [14–17,22].

Th17 and Treg cells may regulate the balance between pro-inflammatory and anti-inflammatory immune responses [22]. Patients with hyper-immunoglobulin E syndrome exhibit Th17 cell deficiencies and are highly susceptible to *Candida albicans* and *Staphylococcus aureus* infections, resulting in skin and lung inflammation [79]. Mutations in the Treg cell master transcription factor-encoding FoxP3 (Figures 1 and 2) result in severe immune dysregulation and autoimmunity in humans (immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome, and increased numbers of Th17 cells) [80,81].

SCFAs may be among the most effective bacterial metabolites involved in the maintenance of the Th cell balance for the host immune responses [22]. In several human immune disorders, such as rheumatoid arthritis and psoriatic arthritis, enhanced Th17 differentiation in the peripheral blood and a decreased abundance of SCFA-producing bacteria in the intestine have been reported. The causal relationship between these factors has been speculated [19,20].

These data will enable the elucidation of the correlation between gut microbiota and immune function in patients with BD.

4.3. Gut Microbiota Profile in Japanese Patients with BD

Gut microbiota analyses were performed with Japanese patients with BD [82,83]. The bacterial species composition was markedly different between patients with BD and healthy donors.

The abundances of the genera *Eggerthella*, *Bifidobacterium*, and *Lactobacillus* were significantly upregulated in patients with BD. Meanwhile, the abundances of the genera *Megamonas*, *Butyrivibrio*, and *Phascolarctobacterium* were significantly upregulated in healthy individuals.

Butyrivibrio species, which were enriched in patients with BD, produce butyrate from wheat bran (dietary fiber) in the in vitro fermentation system of human microbiota [84]. *Phascolarctobacterium* species produce propionate [85] by utilizing lactate [86]. *Bifidobacterium* and *Lactobacillus* species are the major lactate-producing bacteria [86].

Recently, lactate-producing, lactate-utilizing, and SCFA-producing bacteria have been suggested to play a role in maintaining the immune equilibrium of the colon through the production of various metabolites [86]. Several bacterial species in the intestine produce lactate, whereas limited numbers of bacteria produce SCFA with some utilizing lactate

for SCFA production [85–87]. Low pH conditions in culture experiments on human gut microbiota resulted in decreased lactate consumption and SCFA concentrations with lactate accumulation (Figure 3) [86–88].

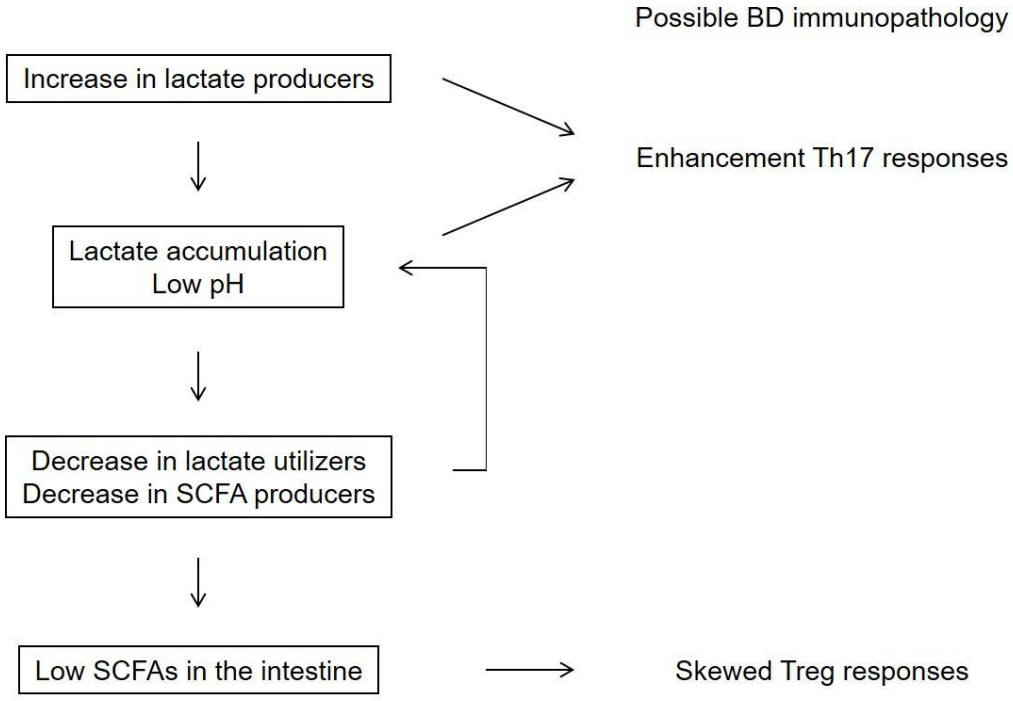

Figure 3. A hypothesis for the mechanism underlying the downregulation of short-chain fatty acids (SCFAs) in the intestine of patients with Behcet's disease (BD). A high prevalence of lactate-producing bacteria may lead to a low pH in the intestine and a decreased abundance of lactate-utilizing bacteria [86]. Lactate-producing bacteria and extracellular lactate were reported to enhance Th17 responses [89,90]. These metabolite processes may be associated with low SCFA concentrations in the intestine and subsequently skewed Treg responses in patients with BD [20].

Lactate is reported to accumulate in the intestine of patients with severe colitis [91,92]. Previous studies have reported that lactate-producing bacteria and extracellular lactate enhance Th17 responses [89,90]. These metabolite processes may be associated with low SCFA concentrations in the intestine and subsequently skewed Treg responses in patients with BD [20].

4.4. Comparison among Countries

The microbiota of patients with BD has been analyzed in other countries [93–98]. The composition of gut microbiota is diverse in human populations [99]. Thus, the microbial profile data of patients with BD are considered valuable. Table 1 summarizes the gut and oral microbial profiles in patients with BD from various countries.

Several lactate-producing gut and oral bacteria have been detected in the microbiota of patients with BD. Meanwhile, several SCFA-producing gut and oral bacteria have been detected in the microbiota of healthy individuals. These data support the hypothesis that intestinal lactate concentrations, SCFA concentrations, gut microbial composition, and skewed T cell responses are correlated in patients with BD. The fecal levels of butyrate in patients with BD are lower than those in healthy individuals [93].

In mouse experiments, orally administered bacteria hardly colonized the intestine, which can be attribute to the competition with commensals [100]. Ingested *Klebsiella* species colonized the intestine and expanded both Th1 cells and IFNγ/IL17-expressing Th cells in the colonic lamina propria in IL10-deficient mice (spontaneous colitis model) [101]. These mechanisms may contribute to the species similarity in the gut and oral microbiota of patients with BD.

Table 1. Summary of the gut and oral microbial profiles in patients with BD in different countries.

	Gut Microbiota				Oral Microbiota		
	Italy, The Netherlands [93,94]	**Turkey [95]**	**China [96]**	**Japan [82,83]**	**The United Kingdom [97]**	**Turkey [98]**	**China [96]**
Abundant in BD	• *Lactobacillaceae*	*Actinomyces* *Eggerthella*	*Bilophila* *Paraprevotella*	*Eggerthella* • *Lactobaccillus* • *Bifidobacterium*	*Rothia* • *Streptococcus*	*Haemophilus* *Alloprevotella*	*Atopobium* • *Lactobaccillus* • *Bifidobacterium*
Abundant in healthy individuals	○ *Roseburia* ○ *Barnesiellaceae* *Subdoligranulum*	○ *Bacteroides* *Alistipes*	○ *Clostridium*	*Megamonas* ○ *Butyrivibrio* ○ *Phascolarctobacterium* *	*Neisseria* ○ *Veillonella* *	*Leptotrichia* ○ *Clostridiales* ○ *Veillonella* *	*Neisseriaceae*

•, Lactate-producing bacteria; ○, short-chain-fatty-acid-producing bacteria; *, lactate-utilizing bacteria [86–88]; BD, Behcet's disease.

4.5. Immunoglobulin-A (IgA) Sequencing (IgA-seq)

Secretory IgA in the intestine is critical for distinguishing commensals from pathogens under the regulation of Th cells [102]. The fecal level of secretory IgA in patients with BD are higher than those in healthy individuals [82]. These data suggest that secretory IgA concentrations in patients with BD are associated with the persistent dysregulation of the intestinal mucosal immune system.

The binding of IgA to gut microbes is assessed using cell sorting, while pathogens are detected using IgA-seq [103]. These analyses have been performed on patients with BD in Italy and the Netherlands [94]. One of the most predominant IgA-coated bacteria in patients with BD belonged to the genus *Bifidobacterium*, a major lactate producer [86] and a prevalent bacterium in Japanese patients with BD [82,83] (Table 1). Replication studies and an understanding of the exact role of secretory IgA in the intestine of patients with BD are required.

4.6. Potential Immunomodulatory Effects of Dietary Supplementation and Herbal Medicine on BD

Various novel therapeutic strategies involving dietary supplementation and herbal medicines are being developed for patients with BD.

The dysregulation of zinc, an essential micronutrient for cellular processes, is reported to be associated with skin manifestations [104]. The serum zinc levels were downregulated and inversely correlated with pathergy test positivity grades in patients with BD when compared with those in healthy individuals [105]. Zinc supplementation improved several activity indices and downregulated the expression levels of toll-like receptor (TLR)-2 [106] and Nod-like receptor-3 (NLRP3) [107] in the white blood cells of patients.

Meta-analyses demonstrated that, compared with those in the control group, the total effective rates of Chinese herbal medicines were higher and the disease recurrence rates were lower in patients with BD [108,109]. The modulatory effects of the herbal medicine decoctions on T cell balance in other human diseases are described in the discussion sections.

A case report on BD revealed that the administration of capsules containing seven strains of live bacteria and concentrated fructo-oligosaccharide, which is one of the most well-studied fermentable dietary fibers [110], gradually ameliorated anterior uveitis [111]. The authors suggested preferable properties of the remedies for the regulation of T cell balance in patients [112].

Recently, a clinical trial was initiated comparing the effects of a vegetarian diet, Mediterranean diet, and Mediterranean diet supplemented with butyrate in patients with BD [113]. Further investigations of food-based interventions are needed to develop new prophylactic or therapeutic strategies for chronic and recurrent inflammatory diseases such as BD.

5. Conclusions

BD is highly prevalent in some areas, which may be attributed to the HLA type. Th cell responses and gut microbiota composition were similar in patients with BD from different

countries as described in this review (Table 1), suggesting that these biological factors are also affected by HLA.

Similar correlations between human immune disorders and HLA molecules have been reported in ankylosing spondylitis and psoriasis, which are classified as MHC class I-opathies. Patients with ankylosing spondylitis and psoriasis have characteristic alterations in the gut microbiota.

Further studies in this field will contribute to the development of novel therapeutic strategies for not only BD but also ankylosing spondylitis and psoriasis based on the modification of intestinal lymphocytes and microbes.

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